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Hempenius, L.; Slaets, J.P.J.; Boelens, M.A.M.; van Asselt, D.Z.B.; de Bock, G.H.; Wiggers, T.; Leeuwen, van, Barbara

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# Inclusion of frail elderly patients in clinical trials: Solutions to the problems<sup>☆</sup>

Liesbeth Hempenius<sup>a,\*</sup>, Joris P.J. Slaets<sup>a</sup>, Mieke A.M. Boelens<sup>a</sup>, Dieneke Z.B. van Asselt<sup>b</sup>, Geertruida H. de Bock<sup>c</sup>, Theo Wiggers<sup>d</sup>, Barbara L. van Leeuwen<sup>d</sup>

<sup>a</sup>University Center for the Elderly, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

<sup>b</sup>Geriatric Center, Medical Center Leeuwarden, The Netherlands

<sup>c</sup>Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

<sup>d</sup>Department of Surgery, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

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## ABSTRACT

With the aging of the population, the interest in clinical trials concerning frail elderly patients has increased. Evidence-based practice for the elderly patient is difficult because elderly patients, especially the frail, are often excluded from clinical trials. To facilitate the participation of frail elderly patients in clinical trials, investigators should be more aware of possible barriers when setting up research. While conducting a trial entitled 'A randomized controlled trial of geriatric liaison intervention in frail surgical oncology patients' (LIFE) the main problem was low inclusion rates. This was due to: 1) limited physical and cognitive reserve of frail elderly patients making participation and extra visits to the hospital a burden for patients; 2) difficulty with understanding written information and information given by telephone; and 3) insufficient awareness of the study by health care professionals. To increase inclusion rates, follow-up measurements were taken at a home visit. To overcome barriers to understanding written information and information given over the phone, patients were informed face to face and questionnaires were filled in an interview format. To increase awareness, posters, pencil and sweets with the logo of the study were distributed and the study protocol was repeatedly explained to new staff. Moreover, it was checked if possible eligible patients coming to the hospital were indeed screened for participation. The mentioned measures, increased inclusion rates but also caused an increased time investment and consequently extra financial resources for staff costs.

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## 1. Introduction

The world's population is aging, with the prediction being that in 2050, when the graying of the population reaches a peak, 27.6% of Europe's population will be over 65 years of age [1]. In the past, elderly patients were often withheld treatment

because of their age. Today, with an increasing elderly population and growing treatment options, physicians are responsible for choosing the optimal treatment for the elderly patient. However, evidence-based practice is difficult because elderly patients, especially the frail, are often excluded from clinical trials [2–4]. The perceived extra burden to frail patients

<sup>☆</sup> Liesbeth Hempenius is a resident in geriatric medicine. The topic of her PhD dissertation concerns the LIFE study: 'A randomized controlled trial of geriatric liaison intervention in frail surgical oncology patients'.

\* Corresponding author at: University Center for the Elderly, University Medical Center Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands. Tel.: +31 503613921; fax: +31 503618888.

E-mail address: [l.hempenius@umcg.nl](mailto:l.hempenius@umcg.nl) (L. Hempenius).

for participating in a clinical trial and the doubt regarding whether the elderly patient might benefit from the trial hamper their inclusion [3,5–8]. To facilitate the participation of frail elderly patients in clinical trials, investigators should be more aware of possible barriers when setting up research. This paper offers an overview of the problems encountered when conducting a randomized controlled trial in a frail elderly population and possible solutions.

## 2. The Trial

This article is based on practical experience gained while conducting a trial entitled ‘A randomized controlled trial of geriatric liaison intervention in frail surgical oncology patients’ (LIFE). The objective of LIFE was to show that a geriatric liaison intervention in frail elderly patients undergoing a surgical procedure for a solid tumor would decrease the occurrence of delirium and consequent morbidity and mortality, without an increase in costs. Three centers participated in this study: center A, a university medical center; center B, a large teaching hospital; and center C, an inner-city hospital.

Patients over 65 years of age undergoing surgery for a solid tumor were assessed with the Groningen Frailty Indicator (GFI) [9] at the outpatient departments of general surgery. The GFI is a short 15-item screening instrument used to determine an individual’s level of frailty. It screens for the loss of functions and resources in four domains of functioning: physical (mobility functions, multiple health problems, physical fatigue, vision, and hearing), cognitive (cognitive functioning), social (emotional isolation), and psychological (depressed mood and feelings of anxiety). Patients with a GFI score greater than 3 are regarded as frail [9,10] and were recruited for this study. Patients with any psychological, familial, sociological or geographical circumstances potentially hampering compliance with the study protocol and follow-up schedule were excluded from participation. Patients unable to fill in the questionnaires were also excluded. From June 2007 to December 2009, 238 patients were included and randomized.

The intervention consisted of a preoperative consultation with a geriatrician and an individual treatment plan targeted at several risk factors for delirium, daily visits by a geriatric nurse during the hospital stay and advice on managing any problem encountered on the basis of a nine-item checklist.

The primary outcome was the occurrence of delirium up to 10 days postoperatively. In both groups the Delirium Observation Scale (DOS) [11] was used to screen for delirium. In the case of a mean DOS score  $\geq 3$  (possible delirium) a geriatrician or psychiatrist examined the patient to confirm the diagnosis according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM IV) criteria.

Data were collected at admission, during the hospital stay and three months after discharge. Patients were asked to complete several questionnaires which was estimated to take 30 min at admission (collection of demographic data, assessment of the quality of life, measured by a Short Form-36 (SF-36) score [12] and care dependency, measured by the Care Dependency Scale (CDS) [13]), 15 min daily during the hospital stay (a nine-item checklist concerning orientation, mobility, anxiety, senses, pain, sleep, intake, defecation and infection

completed by a research nurse), 15 min at discharge (SF-36 and CDS), and 15–30 min for 3 months postoperatively (SF-36, living situation).

Funding was obtained from the Netherlands Organisation for Health Research and Development, trial number 945-07-516. The study was approved by the Medical Ethical Committee of the University Medical Center Groningen (UMCG).

## 3. The Main Problem: Inclusion

In the surgical ward of university center A, a minimum of 180 patients aged 65 years and over are treated for a solid tumor each year. In a prospective study, 85 consecutive admissions for oncological surgery in UMCG were assessed with the GFI and 30% of these patients had a score greater than 3. Based on this pilot study, it was expected that one-third of these patients would be frail. With an expected inclusion rate of 90%, it was calculated that around four patients from center A could be included per month. After similar calculations this number amounted to four patients per month from center B and two from center C. Financial support was available for a total of 30 months: from April 2007 to October 2009. During the course of the study it became clear that the actual inclusion rate fell short of expectations (see Figs. 1 and 2).

## 4. Reasons for Low Inclusion Rate and Possible Solutions

### 4.1. High incidence of refusal to participate

From June 2007 to December 2009, 1256 patients were screened and 359 (28.6%) were found to be frail. Thirty-eight patients failed to meet the inclusion criteria (10.6%). Of the remaining 321 eligible patients, 238 (74.1%) were randomized. This was much less than the expected inclusion rate of 90%. The most important reasons for not entering the study were the refusal to participate ( $n=54$ ; 16.8%) and logistics (planning and transportation) ( $n=12$ ; 3.7%) (Fig. 3).

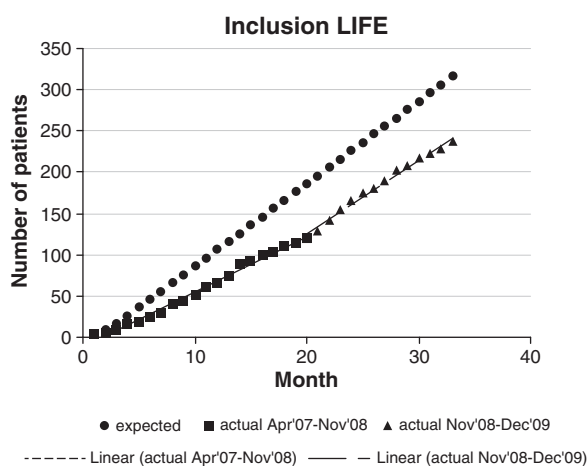
It appeared that patients refused to participate primarily because they felt overburdened by their physical condition, stress, and concerns about the future after the cancer diagnosis. Additional visits and travel to the hospital also discouraged them from participation. This latter problem was solved by home visits and flexible scheduling; for example, appointments related to the study were combined with a scheduled appointment at the hospital to prevent unnecessary travel. In addition, many elderly reported that they did not want to be a burden to their relatives by asking to be accompanied. In general, family members had a major influence on the decision to participate. The approval or rejection of relatives largely determined the decision of a frail older patient to participate in the trial. For this reason, relatives were involved in the informed consent process which took place when the research nurse visited eligible patients and their accompanying relatives at the outpatient clinics. The research nurse was able to give them information in a face to face meeting and gave them the opportunity to ask questions.

#### 4.2. Communication problems

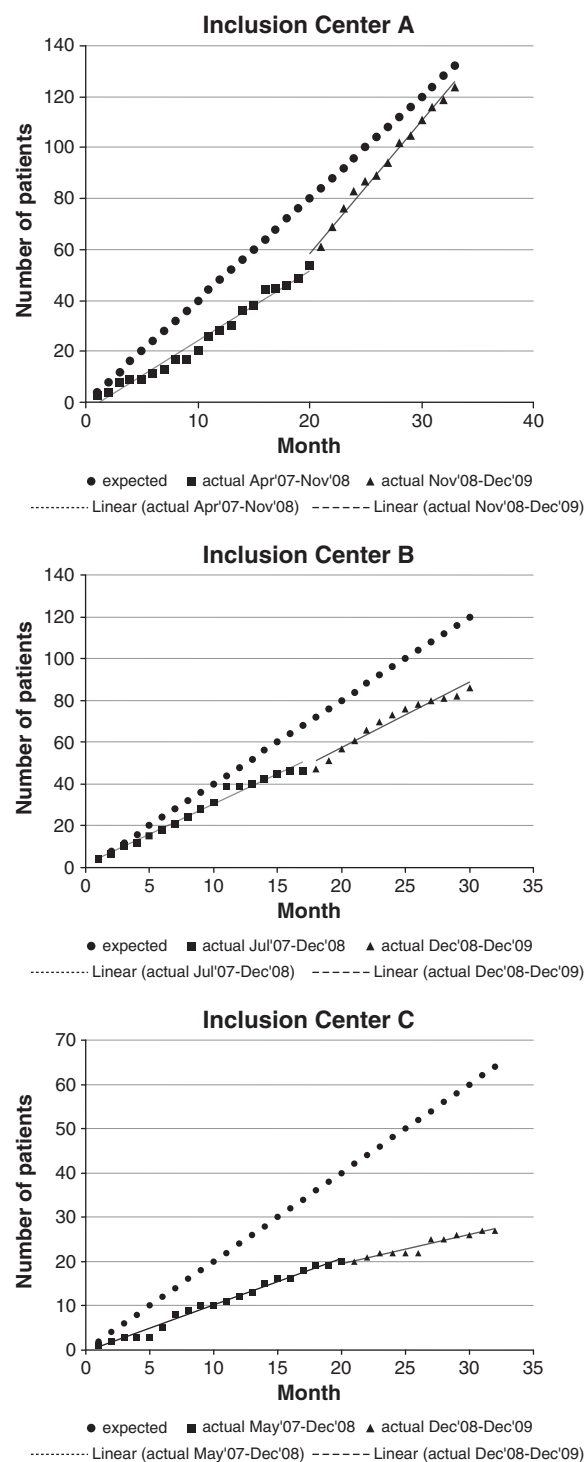
In center A the inclusion rates were lower than expected because of problems in the initial communication process. A research nurse was appointed who had vast research experience, but no specific experience in the care for and communication with the elderly patient. Potential eligible patients were informed about the study by nurses on the outpatient clinics. Often only written information was given. Afterwards patients were contacted by telephone by the research nurse for participation. When a patient decided to participate, informed consent had to be returned by post, which was an additional barrier.

In this population it is important to take extra time when communicating, as communicative capacity is often restricted because of a higher incidence of sensory loss (hearing and visual problems), speech problems such as aphasia and dysarthria and cognitive decline. In our experience it is by far more preferable to communicate with patients face to face as they seem to understand information given in this way much better than by telephone. Jansen (2009) studied communication between the older patient with cancer and clinician [14] and found that patients are better able to recall information when: 1) only the most important information is discussed with the elderly patient and the duration of a consultation is limited; 2) a companion is present during the consultation — a patient who prefers to be accompanied should be stimulated to bring someone with them; 3) empathy is expressed when a patient shows emotion. These recommendations should be taken into account when communicating with older adults.

After persistent disappointing inclusion rates, it was decided that a nurse with ample experience in caring for and communicating with elderly patients should be appointed. Her efforts increased the inclusion rate substantially from December 2008 (see Fig. 2). She was informed when there was an eligible patient on the outpatient clinic and then visited the patient immediately at the outpatient clinic visit to give them face to face information. Then questions of the patient and relatives could be answered and informed consent could be signed if the patient decided to participate.



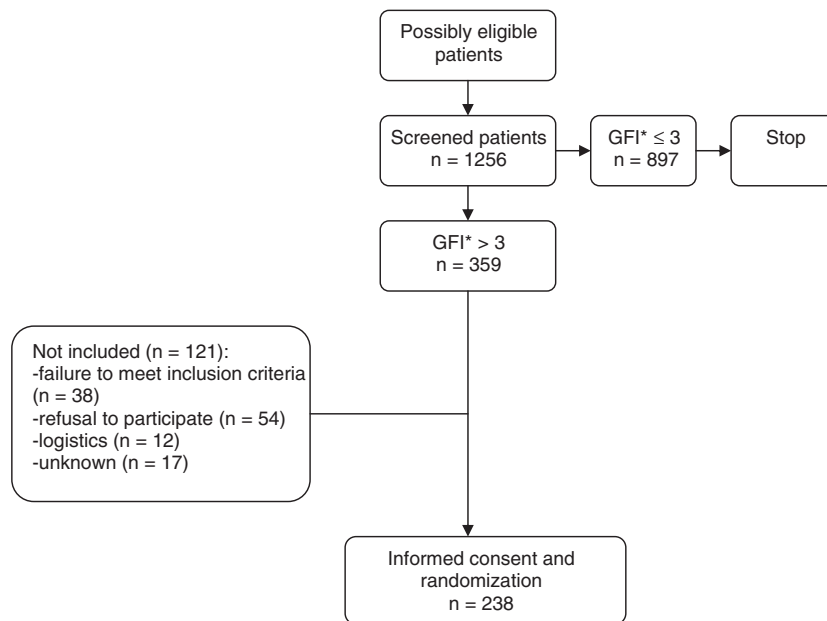
**Fig. 1 – Expected versus actual inclusion in the LIFE study. Trend lines and formula added for the actual inclusion rates from April 2007 to November 2008 and from November 2008 to December 2009.**



**Fig. 2 – Inclusion per center. Trend lines added for the actual inclusion rates for the first and second parts of the study.**

#### 4.3. Relocation of frail patients

Unexpectedly, frail patients were often operated on in the university hospital near center C. Because the participation of center C was not cost-effective, funding was partly withdrawn and the inclusion of patients from this center ended prematurely.



**Fig. 3 – Flow chart of inclusion rates. \*GFI = Groningen Frailty Indicator, a screening instrument used to determine an individual's level of frailty. Patients with a score greater than 3 were regarded as frail and were recruited for this study.**

#### 4.4. Staff insufficiently aware of the study

In all centers it became apparent that 10–20% of eligible patients were not screened. To increase general awareness of the study, posters, pencils and sweet jars with the logo of the study were distributed to the outpatient clinics and wards. During the following months every patient that visited the outpatient clinic and was possibly eligible for LIFE was marked in the patient list by the research nurses. Afterwards it was checked if these patients were indeed screened. Also, weekly reports of screening results were presented to the nursing staff involved. In addition, because all surgical patients were discussed in multidisciplinary meetings before treatment, patient lists of these meetings were checked weekly to detect unscreened patients.

In center B, the study started months later than planned. While the start of the study was agreed to by all medical staff, the nurses were poorly informed. The success of this study depended largely on the commitment of nurses in the outpatient clinics and the wards.

Again it became clear that supplying adequate information and instructions to the health care professionals involved benefited the progress of the study. For both doctors and nurses, clinical research often means that there are additional tasks to do alongside their daily care activities. Our experience indicates that the research tasks usually are low in priority, especially when the provision of information is poor. It is preferable to plan time for research tasks in the usual schedule. It is also desirable to repeatedly explain the study protocol and continue to remind existing staff and instruct new staff in this regard. We realize that this problem is not specific to research in a frail elderly population, but is important for clinical research in general.

An additional measure taken to increase the inclusion rate was the involvement of the departments of gynecology; ear, nose and throat medicine; and maxillofacial surgery in centers

A and B. This required further investment of time and resources to inform and educate the staff.

Due to the above-mentioned measures, the inclusion rates increased in centers A and B. The trend in the inclusion rate for the second part of the study shows an increased slope in comparison with the first part (Fig. 2). In center C the inclusion rate decreased during the second part of the study (Fig. 2). One reason was that the geriatrician responsible for the study moved to another hospital. Additionally, the distance between center C and center A (the work location of the primary investigator) made intensive supervision difficult. These factors may have influenced the low inclusion rate in center C.

After 30 months the estimated number of patients had not yet been recruited, resulting in a prolonged inclusion phase of 8 months and the redistribution of financial resources. Due to the disappointing results in center C, the inclusion phase and financial support were not prolonged there.

## 5. Other Problems and Solutions

Although the inclusion of frail elderly patients in this trial proved to be the biggest problem, we encountered several other issues influencing the success of this study.

### 5.1. Sample size calculation: estimating incidences was difficult due to the heterogeneity of the population

To achieve a power of 80% with an  $\alpha$  of 5% (one-sided), a  $\beta$  of 95% and an expected drop-out rate of 10%, a total inclusion of 294 patients was calculated for this study. The reported incidence of delirium varies widely between and within the populations under investigation. Incidences vary from less than 10% up to 50% after orthopedic [15], abdominal [15,16] and cardiac surgery [17]. Based on these data the incidence of delirium in our



population was assumed to be 30%. Because we studied a high risk population, we thought that an incidence of 30% was a conservative estimate. We expected to find an absolute reduction of 15%. Based on the results of Inouye (1999), we felt that aiming for a total reduction of 15% (and thus a final incidence of 15%) would be feasible [18]. Inouye et al. found a final incidence of 10%.

The preliminary results of the LIFE study showed an unexpectedly lower overall incidence of delirium than expected. A great variance in outcome measures is inherent to the elderly population due to heterogeneity with respect to physical, mental and social functioning. We recommend using cautious estimates of incidence when calculating sample size in this population to maintain power.

## 5.2. Time management

All parts of the trial (recruitment, intervention, measurements and analysis) took more time than anticipated and, consequently, more financial resources than calculated. We had calculated an overall mean time investment of 2 h per patient but the actual time investment per patient amounted to be more than 6 h. Since patients in this population have difficulty interpreting self-administered questionnaires, the questions were administered in an interview form. Studies have shown that frail older adults have difficulty with self-administered questionnaires. For example, the Short Form-36 (SF-36) [12] has proven to be reliable and valid in a frail elderly population only when used in an interview setting [19,20].

The interview setting used made it difficult to strictly adhere to the content of the questionnaires due to the addition of personal comments and questions leading the patients to disclose tangential information. This contributed to the questionnaires taking more time than anticipated. In addition, in the course of the study some questionnaires were added to the protocol, namely the Mini-Mental State Examination (MMSE) [21] to measure preoperative cognitive functioning and 3 months after, the Geriatric Depression Scale (GDS) [13] to measure preoperative depression, and the Mini Nutritional Assessment — Short Form (MNA-SF) [22] to measure preoperative malnutrition.

The additional visit to the hospital for the follow-up measurement at three months was a stressful experience for many patients. It was necessary to adapt the research protocol to allow visits to the home for this measurement, taking into account the patients' physical and cognitive abilities. The travel time needed increased the time investment per patient considerably.

## 6. Other Potential Pitfalls

Beyond the problems we encountered while conducting the LIFE study there are other potential pitfalls. We want to emphasize the importance of the selection of patients. Patients who are too frail or too fit should be excluded to optimize internal validity (the need to focus the study group to maximize the chances of detecting an impact of the intervention if it exists). However, eligibility criteria should not be too strict with respect to external validity (the ability to generalize to a larger population) [5]. For example, in the LIFE study, patients

unable to understand questionnaires were excluded, although patients with decreased cognitive abilities are at high risk to develop delirium. Furthermore patients undergoing surgery for a superficial tumor (skin, breast) were included in the study, although they are at low risk to develop postoperative delirium. Both criteria may have lowered the delirium incidence rate in our study and reduced the change to show effectiveness of the intervention.

Moreover, problems with judging decision-making capacity due to cognitive impairment may be a barrier to the inclusion of frail older adults in clinical trials. The gold standard for making a judgment about capacity is an evaluation of the criteria for decision-making capacity in a semi-structured interview [16]. We did not use this in our study, but it seems to be a useful tool for inclusion of elderly patients with cognitive impairment in clinical trials.

## 7. Conclusion

Executing a clinical trial in frail elderly patients requires an adjusted approach. When designing a protocol and scheduling measurements, physical (mobility problems, sensory losses and reduced exercise capacity) and mental abilities (cognitive impairments) of frail elderly patients should be evaluated and taken into account. Members of the research team should have an affinity with the elderly population and be aware of the fact that extra time and financial resources are needed when conducting research in a frail elderly population.

## Disclosures and Conflict of Interest Statements

None.

## Author Contributions

Concept and Design: B. van Leeuwen, J. Slaets, T. Wiggers, T. de Bock.

Data Collection: B. van Leeuwen, L. Hempenius, M. Boelens.

Analysis and Interpretation: L. Hempenius, T. de Bock, B. van Leeuwen, J. Slaets, T. Wiggers.

Manuscript Writing and Approval: L. Hempenius, B. van Leeuwen, J. Slaets, M. Boelens, D. van Asselt, T. de Bock, T. Wiggers.

## Ethical Approval

The study was approved by the Medical Ethical Committee of the University Medical Centre Groningen, trial number NL 15136.042.06.

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